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| 10/523,858 | 04/01/2005 | Anne Elizabeth Bishop | 233752 | 8651 |

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| EXAMINER | |
|---|---|
| BARNHART, LORA ELIZABETH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

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|---|---|
| 08/08/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/523,858 | BISHOP ET AL. | |
| | Examiner | Art Unit | |
| | Lora E. Barnhart | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2008 and 14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendments*

Applicant's amendments filed 4/14/08 to claim 1 have been entered. Claims 3, 5, and 7-21 have been cancelled. No claims have been added. Claims 1, 2, 4, and 6 remain pending in the current application, all of which are being considered on their merits. Prior art references not included with this Office action can be found in a prior action. Applicant's arguments submitted 3/5/08 (which were accompanied by a claim listing that did not comply with 37 C.F.R. 1.121) are also being considered at this time.

### *Specification*

The objection to the form of the specification is withdrawn in light of the submission of a substitute specification.

The amendment filed 3/5/08 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: At page 1 of the marked-up copy of the substitute specification, a paragraph has been inserted; applicant should particularly point out the basis for this new paragraph in the as-filed specification. Furthermore, a line was added at the bottom of page 12 of the marked-up copy of the substitute specification that explicitly broadens the scope of the disclosure, since it characterizes the Examples as non-limiting. Applicant is required to cancel the new matter in the reply to this Office Action or to point out basis for these insertions in the as-filed specification (not the published application).

***Claim Rejections - 35 USC § 112***

Any rejection of record under 35 U.S.C. § 112 not specifically discussed below is withdrawn in light of the claim amendments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 4 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of differentiating embryonic stem (ES) cells into cells that express surfactant protein C (SPC) by culturing the ES cells such that they form embryoid bodies and then culturing these embryoid bodies in a particular medium comprising particular amounts of particular growth factors, does not reasonably provide enablement for differentiating any stem cell into SPC-expressing cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention

based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to a method in which any stem cell is cultured under conditions that promote the formation of embryoid bodies and in which said embryoid bodies are subsequently cultured under conditions that promote their differentiation to SPC-expressing cells; these conditions include exposure to some unnamed "differentiation factors" and subsequent culturing in SAGM medium. The claim does not describe either the conditions for the formation of embryoid bodies or the differentiation factors that would promote the transformation. This breadth is not supported by the teachings of the specification in view of the art.

The cited claims do not place any limit on the type of stem cell to be employed in the method. Even after the time of the invention, however, differentiating a given stem cell type into lung cell types is not considered routine experimentation although the level of ordinary skill is postdoctoral. For example, van Haaften et al. (2006, *Pediatrics Research* 59 Supplement: 94R-99R) teach that while some reports indicate that mesenchymal stem cells (MSCs) can engraft into lung tissue and differentiate into lung cells (page 96R), other results show that implanted MSCs do not adopt the type II alveolar epithelial cell phenotype (page 97R). Van Haaften concludes that stem cell therapy for lung diseases is at the conceptual stage and is a continuing problem in the art of these diseases (page 98R).

M.P.E.P. § 2164.03 reads, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the

art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** See, *e.g., Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)...In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required." As the above discussion illustrates, the art of differentiating stem cells into lung cells was unpredictable at the time of the invention, so this art must be considered "nascent," and the amount of guidance required is relatively high.

Finally, applicants present a single working embodiment in which ES cells are cultured in suspension to yield EBs and then cultured in SAGM to yield SPC-expressing cells (see page 12 of the as-filed specification). Applicant provides no particular guidance for using any other kind of cell; the statement at page 4, lines 12-17, that the stem cell can be "any pluripotent or multipotent stem cell" is not supported by the specification or the art, which even years after the invention remains unpredictable.

There is no evidence that at the time of the invention, the skilled artisan could have cultured any stem cell other than an ES cell in SAGM medium to yield SPC-expressing cells. While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

Applicant alleges that the specification teaches that any stem cell may be used (Reply, page 5, second-to-last paragraph). Applicant supplies a reference that allegedly enables the invention (Reply, page 6, last paragraph et seq.). These arguments have been fully considered, but they are not persuasive.

The portion of the specification to which applicant refers in the reply (page 4, lines 12-17, of the as-filed specification) does not contain any specific guidance as to how to adapt the exemplified method to each and every stem cell, which is the scope of the claims. The passage at page 4 constitutes nothing more than a nonspecific plan to extend the scope of the invention; as discussed above, in unpredictable arts such as this one, this is insufficient guidance.

The Berger reference is noted, but this reference was published many years after the instant filing. However, M.P.E.P. § 2164.05(a) requires that the specification be enabling **as of the filing date.** The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the

filing date. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). A later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling. *Gould v. Quigg*, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987). Therefore, in the absence of expert testimony indicating that Berger reflects the state of the art at the time of filing, the reference cannot overcome this ground of rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, and 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 requires that the EBs yielded by step (a) be exposed to "differentiation factors" and also that they be cultured "in the presence of SAGM medium." However, SAGM medium includes growth and differentiation factors (see page 12, lines 29-33). It is not clear whether the "exposing" and "culturing" steps are two different steps or whether a step in which EBs are cultured in SAGM (but no additional differentiation factors) would be encompassed by the claim. Clarification is required.

Claim 1 recites "culturing the stem cell to give an embryoid body," which is confusing because it does not particularly point out or distinctly claim the conditions necessary to effect this change. It is noted that the claim requires that the EB be "exposed to differentiation factors," but it is not clear that this amendment addresses the issue, as the claim does not particularly indicate the conditions for culturing EBs from stem cells.

Claim 1 also recites the limitation "conditions which cause [the EB] to differentiate into cells which express surfactant protein C," which also does not particularly point out the conditions. It is not clear that one skilled in the art could determine specific conditions based on the disclosure for each and every type of stem cell. See *In re Mattison*, 509 F.2d 563, 184 USPQ 484 (CCPA 1975). Clarification is required.

Because claims 2, 4, and 6 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Regarding the rejection of record under § 112, second paragraph, applicant alleges that the post-filing Berger reference defines the conditions (Reply, page 6, second-to-last paragraph). However, this reference is not pertinent to the interpretation of the claims at the time of the invention, since it was published many years afterward. The remainder of applicant's comments are a *per se* allegation that the claims are definite, but they do not point out guidance that the skilled artisan could have used at the time of the invention to determine the claimed conditions, factors, and so on.

***Claim Rejections - 35 USC § 102***

Any rejection of record under 35 U.S.C. § 102 not specifically discussed below is withdrawn in light of the claim amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4, and 6 remain rejected under 35 U.S.C. 102(a) as being anticipated by Ali et al. (2002, *Tissue Engineering* 8: 541-550; reference AC on IDS). The claim term "SAGM" is interpreted as it is defined at page 12, lines 29-33, of the as-filed specification.

Ali teaches a method that comprises culturing ES cells in suspension (*i.e.*, on nonadherent culture dishes) to yield EBs, then culturing the EBs in SAGM, which comprises differentiation factors including EGF (page 542, last paragraph under "Cell culture" continued to page 543). The method of Ali yields cells that express SPC (Figure 2a, lanes 3 and 4; and page 545, first two paragraphs under "SPC mRNA expression").

Applicants allege that Ali does not qualify as prior art under 35 U.S.C. § 102(a) because it was not publicly available before the filing of the foreign priority document and supply informal correspondence from the British Library as evidence (Reply, page 7, paragraph 3). These arguments have been fully considered, but they are not persuasive.

37 C.F.R. 1.132 reads, "When any claim of an application or a patent under reexamination is rejected or objected to, any evidence submitted to traverse the rejection or objection on a basis not otherwise provided for must be by way of an oath or declaration under this section." In other words, any evidence submitted to overcome the pending art rejection must be properly submitted as an affidavit, not merely enclosed as a portion of applicant's comments. However, if the evidence from the library were properly submitted as an affidavit, it would disqualify Ali as prior art under § 102(a).

***Allowable Subject Matter***

If the Ali reference were properly disqualified as prior art as discussed above, and the issues under § 112, second paragraph, were resolved, claim 6 would be allowable if rewritten in independent form.

***No claims are allowed. No claims are free of the art.***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651